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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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PILLSBURY WINTHROP, LLP
P.O. BOX 10500
MCLEAN, VA 22102

EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	**PAPER NUMBER**
1644	

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29

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No. 09/435992	Applicant(s) HANNA ET AL.
	Examiner GAMBEL	Art Unit 1644

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☑ A Notice of Appeal was filed on 1/10/03. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☑ The proposed amendment(s) will not be entered because:

   (a) ☑ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☑ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☑ The a)☐ affidavit, b)☐ exhibit, or c)☑ request for reconsideration has been considered but does NOT place the application in condition for allowance because: OF THE REASONS OF RECORD.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☑ For purposes of Appeal, the proposed amendment(s) a)☑ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: 60-85

   Claim(s) withdrawn from consideration: _____.

PHILIP GAMBEL
PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
TECH CENTER 1600
3/7/03

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

U.S. Patent and Trademark Office
PTO-303 (Rev. 04-01) Advisory Action Part of Paper No. 29

APPLICANT'S REQUEST FOR WITHDRAWAL OF FINALITY WITH RESPECT TO THE ELECTED INVENTION IS NOT FOUND CONVINCING AS THE SUBJECT OF THE OFFICE ACTIONS AS THEY READ ON THE ELECTED SPECIES HAS BEEN OF RECORD. IF APPLICANT DID NOT AGREE WITH THE ELECTED SPECIES AS INDICATED PREVIOUSLY, APPLICANT SHOULD HAVE RAISED SUCH CONCERNS PREVIOUSLY AND NOT AFTER FINAL. FOR EXAMPLES, SEE PAPER NO. 18 FOR HOW CLAIMS WERE READ. IN REVIEWING PROSECUTION NO PREVIOUS OBJECTIONS BY APPLICANT WERE NOTED

IT APPEARS, IF ENTITLED, THE DEPOSIT OF JDEC C2B8 AND 24-31 MAY BE SATISFIED BY INCORPORATION OF REFERENCE TO U.S. PATENTS. THIS WILL BE REVISITED.

PAPER NO. 29

DETAILED ACTION

1. Applicant's amendment, filed 4/22/02 (Paper No. 20), has been entered.
Claims 1-41 and 57-59 have been canceled. Claims 42-56 have been canceled previously.
Claims 60-85 have been added.

Applicant's election of Group I as it reads on the combination of anti-CD40L antibody and anti-CD20 antibody and leukemia as the $CD40^+$ malignancy in Paper Nos. 11 and 17 has been acknowledged.

Applicant further elected ^{90}Y and alkylating agents as the chemotherapeutics in combination with the elected species.

For the purposes of this Office Action, the anti-CD20 antibody is radiolabeled (e.g. ^{90}Y) and anti-CD40L antibody is not radiolabeled.

This election of an anti-CD20 antibody which is radiolabeled (e.g. ^{90}Y) and an anti-CD40L antibody which is not radiolabeled appears consistent with the Examples set forth in the instant specification and the election of leukemias rather than lymphomas.

Claims 60-85 are under consideration in the instant application, as they read on the elected invention/species.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed 4/22/02 (Paper No. 20).
The rejections of record can be found in the previous Office Action (Paper No. 18).

3. Applicant's provision of Figures 1-4 in conjunction with the Hariharan affidavit who attests to the fact that these Figures are the same Figures described in the as-filed application, filed 4/22/02 (Paper No. 20), is acknowledged.

However, this is an issue for the Office of Petitions. Therefore, after this Office Action is mailed, it will be sent to the Office of Petitions with respect to the missing Figures.

4. Applicant's newly submitted claims, filed 4/22/02 (Paper No. 20), have obviated the previous rejection under 35 U.S.C. 112, first paragraph, scope of enablement as the claims read on "CD20-specific antibodies" and "CD40L-specific antibodies"

5. Claims 66 and 68:

It is apparent that IDEC-131 and RITUXAN antibodies are required to practice the claimed invention. As required elements, they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the pertinent cell lines / hybridomas which produce these antibodies. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

Applicant's amendment, filed 4/22/02 (Paper No. 20), relies upon the allowance of the humanized anti-CD40L antibody IDEC-131 in a copending application and on the commercial availability of RITUXAN as well as U.S. Patent Nos. 5,776,456 and 5,843,849.

However, applicant has not made it clear which deposited and claimed antibody / hybridoma reads on IDEC-131 and RITUXAN, nor has provided evidence of commercial availability of these antibodies.

Again, it is noted that certain of these antibodies are claimed in U.S. Patents (e.g. see art rejections below) which would be indicative, but not necessarily mean (see MPEP 2404.01) that the enablement of biological materials under 35 USC, 112, first paragraph, has been satisfied.

Applicant is required to indicate which antibodies are enabled accordingly and to satisfy the deposit of the biological materials for the others accordingly.

6. Claim 68 is objected to because "I?DEC-131" should be "IDEC-131".

Claim 69 is objected to because "Cd20" should be "CD20".

Applicant is invited to carefully review the designations and spellings of the chemotherapeutics set forth in claims 72 and 77-79. For example, it appears that "CHOP<C-MOPP" is a misprint.

7. Claims 66 and 68 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 66 and 68 are indefinite in the recitation of "IDEC-131 (I?DEC-131)" and Rituxan® because their characteristics are not known. The use of these "designations" as the sole means of identifying the claimed antibodies renders the claims indefinite because these are merely laboratory designations which do not clearly define the claimed products, since different laboratories may use the same laboratory designations to define completely distinct cell lines .

Claims 66 and 68 contain the trademark or trade name "RITUXAN" and "IDEC-131 (I?DEC-131"). Where a trademark or trade name is used in a claims as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 USC 112, second paragraph, See Ex parte Simpson, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark or the trade name "RITUXAN" or "IDEC-131" is used to identify or describe an antibody, and accordingly, the identification or the description is indefinite. The relationship between a trademark or tradename and the product it identifies may be uncertain and arbitrary. The formula or characteristics of the product may change from time to time and yet it may continue to be sold under the same trademark or tradename.

Amending the claims to recite the appropriate ATCC Accession Numbers would obviate this rejection

The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

8. Claims 60-85 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kaminski et al. (U.S. Patent No. 6,287,537) AND/OR Anderson et al. (U.S. Patent No. 5,843,439) in view of Smiers et al. (Br. J. Haematol. 93: 125-130, 1996), Schattner et al. (Blood 91: 2689-2697, 1998), Gruss et al. (Leukemia and Lymphoma 24: 393-422, 1997), Renard et al. (Blood 87: 5162-5170, 1996), Black et al. (U.S. Patent No. 6,001,358), Noelle et al. (U.S. Patent No. 5,747,037) in view of standard chemotherapeutic treatments, including combination therapy of leukemias known and practiced by the ordinary artisan at the time the invention was made, as acknowledged on pages 39-40 of the instant specification.
essentially for the reasons of record set forth in Paper No. 18.

Applicant's arguments, filed 4/22/02 (Paper No. 20), have been fully considered but are not found convincing essentially for the reasons of record.

Applicant argues that none of the references suggest the combined use of an anti-CD40L antibody and an anti-CD20 antibody to treat a B cell leukemia as claimed.

While applicant acknowledges that combined therapies are routine in treating malignancy, applicant asserts that this relates to the combined use of radiotherapy and chemotherapy and not the combined administration of different antibodies. Applicant also relies upon the approval of Rituxan as the first antibody for any B cell malignancy to attest to the unpredictability of using antibodies for therapy, including in the treatment of B cell malignancies.

Applicant asserts that the treatment with an anti-CD40L antibody, including IDEC-131, as well as the anti-CD20 antibody Rituxan renders malignant B cells more susceptible to the effects of chemotherapeutic agents(e.g. adriamycin).

Applicant asserts that the synergistic benefits achieved by applicant's therapeutic regimen are not fairly suggested by the prior art.

Synergism is a very broad term and means the combined action of two or more agents which is greater than the sum of the action of one of the agents used alone. However, it is noted that applicant has not pointed out the support in the instant disclosure for synergistic benefits of the claimed invention or the support in the instant disclosure for synergistic benefits commensurate in scope with the claimed invention.

Further, it is noted that page 41, paragraph 2 of the instant specification acknowledges that the skilled artisan is readily credited with assessing a particular patient and determining a suitable dosage that falls within the range, or if necessary, outside the range as needed. Therefore, if applicant is relying upon certain dosages of anti-CD20 antibodies and anti-CD40 antibodies to meet the asserted synergistic benefits, it appears that the specification as filed acknowledges that suitable dosages were well within the skills of the ordinary artisan at the time the invention was made.

The following of record is reiterated for applicant's convenience and to address applicant's arguments.

Kaminski et al. teach the use of anti-CD20 antibodies, including radiolabeled anti-CD20 antibodies (e.g. B1) in combination with other treatments to treat B cell malignancies (see entire document, Summary of the Invention and Detailed Description of the Invention). Kaminski et al. teach the art known expression of CD20 on B cell leukemias (column 4, paragraph 1).

Anderson et al. teach the use of anti-CD20, including radiolabeled anti-CD20 antibodies (e.g. 2B8 / RITUXAN) in cooperative strategies to treat B cell malignancies (See entire document). Anderson teach that the anti-CD20 antibody 2B8 was raised against the human acute lymphoblastic line SB (column 12, 2B8).

Therefore, the prior art taught combination therapy to various B cell malignancies, including B cell leukemias with radiolabel CD20-specific antibodies, including B1 and RITUXAN at the time the invention was made. Both references teach the use of art known radiolabels including ^{90}Y for radioimmunotherapeutic antibodies (see entire documents), encompassed by the claimed methods. Therefore, the claimed labels (e.g. claim 13) were known and routinely practiced at the time the invention was made.

Therefore, the prior art does teach the use of the particular Rituxan anti-CD20 antibody in treating B cell malignancies at the time the invention was made.

The references do not teach the use of radiolabeled CD20-specific antibodies in combination with CD40L-specific antibodies.

Smiers et al. teach that is was known at the time the invention was made that B cell leukemias expressed both CD20 and CD40 and leukemic cells proliferate in response to either CD20 or CD40 activation (see entire document, including Discussion).

Schattner et al. teach that CD40L is expressed on certain chronic lymphocytic leukemias and is important factor in CLL tumor growth as well as an important factor in the generation of pathologic antibody in some patients with CLL (see entire document, including Abstract and Discussion). Schattner et al. also teach that is was known at the time the invention was made that B cell leukemias expressed both CD20 and CD40 (see Abstract).

Gruss et al. teach that CD40 is expressed on B cell leukemias and that the CD40:CD40L pathway, including CD40L-expressing T cells, which are readily detectable around neoplastic B cells, enhance B cell activation and growth (see pages 404-405, B cell Lymphomas and Lymphoproliferative Disorders). It is noted that Gruss et al. teach the therapeutic use of recombinant CD40L rather than CD40L-specific antibodies as inhibitors of malignant B cell growth (page 404, column 1). While Gruss et al. disclose the art known formation of neutralizing anti-mouse antibodies as a limitation of antibody therapy, such limitations have been long addressed by the use of recombinant antibodies such as humanized antibodies, known and practiced in the art for a decade (also, see Noelle et al. and Black et al. herein).

Renard et al. teach autologous $CD4^+$ T cells isolated from leukemia patients were able to induce CD40-dependent proliferation of B cell leukemic blasts (see entire document, including the Abstract). Also, this proliferative response was inhibited by anti-CD40L antibody (see Results).

Therefore, the prior art of Schattner et al., Gruss et al. And Renard et al. taught the importance of CD40L-mediated interactions in B cell leukemia and clinical manifestation. Also as pointed out above, Gruss et al. does teach that CD40:CD40L interactions are par of cellular activation and neoplastic tumor cell growth which would be useful for the therapeutic management of $CD40^+$ tumors (see page 404, column 1).

Therefore, the prior art does provide motivation and expectation of success in combining antagonists of CD40:CD40L interactions in addition to targeting CD20 in the treatment of B cell malignancies, such as leukemia.

Gruss et al. does not teach the art known CD40L-specific antibody antagonists, including the antibody species encompassed by the claimed invention.

Black et al. teach the use of gp39/CD40L-specific antibodies, including recombinant antibodies and antibody fragments, to inhibit CD40:CD40L interactions or where gp39 inactivation and/or modulation of the gp39(CD40L)/CD40 interaction is desirable (e.g. column 11, lines 34-39 and column 14, lines 35-38). (see entire document, including Summary of the Invention and Detailed Description of the Invention). In addition, Black et al. teach the antibody species 24-31 (e.g. IDEC-131), encompassed by the claimed invention (see entire document, including Summary of the Invention, Detailed Description of the Invention and Claims).

Noelle et al. teach gp39- /CD40L-specific antibodies (e.g. see column 3, paragraph 3 and column 4, paragraph 2) encompassed by the claimed invention (e.g. claim 7), which are useful for in inhibiting the interaction between gp39/CD40L with its ligand CD40 (see entire document, including Summary of the Invention and Detailed Description of the Invention). In addition, Noelle et al. teach the art known use of recombinant antibodies and antibody fragments (e.g. see gp39 Antagonists, column 6-9), encompassed by the claimed invention (e.g. claims 8 and 9).

Black et al. and Noelle et al. both teach the art known advantages of recombinant antibodies and antibody fragments as therapeutic agents (see Detailed Description of the Invention), given their decreased immunogenicity compared to their native murine antibody counterparts and ease of production and homogeneity.

The instant specification acknowledges standard chemotherapeutic treatments of leukemias, including combination therapy was known and practiced by the ordinary artisan at the time the invention was made (see pages 39-40 of the instant specification). Therefore, the chemotherapeutic agents including the alkylating agents employed in the claimed methods was obvious, given their standard use by the ordinary artisan at the time the invention was made.

Given the teachings of Kaminksi et al. to employ radiolabeled antibodies in combination with other treatments to treat leukemia as well as the acknowledgment by applicant that combination therapy was known and practiced in the art at the time the invention was made, one of ordinary skill in the art would have been motivated to treat B cell leukemia with a combination of therapies.

Given the expression of CD20 and CD40 and the ability of activation via CD20 and/or CD40, the ordinary artisan would have been motivated to target B cell leukemia directly with radiolabeled CD20-specific antibodies and to diminish activation of said B cell leukemia by blocking activation with CD40L-specific antibodies.

One of ordinary skill in the art would have employed non-radiolabeled CD40L-specific antibodies, given the expression of CD40L on normal activated T cells and the role of such CD40L on such T cells to stimulate CD40-expressing B cell leukemic cells, as taught above.

Radiolabeled CD40L-specific antibodies would target and kill non-malignant T cells.

Also, Schattner et al. teach that the CD40L expressed on certain B cell leukemic cells played a role in B cell leukemic and autoimmune manifestations in leukemia patients.

Also as pointed out above, Gruss et al. does teach interrupting CD40:CD40L interactions to inhibit tumor cell activation and growth.

Given the standard regimen of chemotherapy in leukemic patients and the teachings of Kaminski et al. to combine standard therapy with radiolabeled antibodies, one of ordinary skill in the art at the time the invention was made to employ multiple modalities to treat B cell leukemia. Given the addition of non-radiolabeled CD40L-specific antibodies, the ordinary artisan would have been administering a less toxic therapeutic regimen, when compared to radiolabeled antibodies and chemotherapeutic agents.

One of ordinary skill in the art at the time the invention was made would have been motivated to select radiolabeled CD20-specific antibodies, non-radiolabeled CD40L-specific antibodies and standard chemotherapeutic to treat B cell leukemia at the time the invention was made, given the teachings above. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments are not found persuasive.

9 Claims 60-85 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over pending claims of copending applications USSN 09/772,938 . Given the election in the instant case, the conflicting claims may or may not be identical, depending upon the invention(s) elected in these copending applications. The claims are not patentably distinct from each other because they appear to read on the same or nearly the same reagents to treat the same or nearly the same leukemias and lymphomas.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

10. No claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
July 8, 2002